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Review Article

Association of PDCD1 gene polymorphisms with systemic lupus erythematosus and lupus nephritis: an up-date meta-analysis

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Abstract: Background: A genome-wide scan has suggested a strongly significant association between chromosome 2q37 gene loci and susceptibility to systemic lupus erythematosus (SLE) and just right the programmed cell death 1 (PDCD1) gene is located on chromosome 2q37, but there is no precise conclusion existing. Aim: To derive a more precise evaluation the association of PDCD1 gene single nuclear polymorphisms (SNPs) with susceptibility to SLE and lupus nephritis (LN) through meta-analysis. Methods: EMBASE and PubMed were exhaustively searched for studies up to September 2015. Begg's funnel plot and Egger's test were performed to assess the publication bias of the literature, and sensitivity analyses were performed to identify heterogeneity. A fixed- or a random-effects model was applied to calculate the pooled odds ratio (OR). Results: The results of the pooled analysis suggested that PD1.3 SNPs were significantly associated with the risk of SLE. When the studies were stratified by ethnicity, a significant association between PD1.3A/G and SLE was observed in Latin [OR=2.961, 95% CI=1.776-4.936, *P*<0.001], but not in Caucasian, African and Asian populations. The PD1.3A allele was a risk factor for LN both in overall and Caucasian descendants [overall: OR=1.776, 95% CI=1.290-2.444, *P*<0.001; Caucasian: OR=1.873, 95% CI=1.341-2.616, *P*<0.001]. Whereas, no significant associations were found between PD1.1, PD1.5 or PD1.6 SNPs and SLE. Conclusions: PD1.3A allele is associated with susceptibility to SLE and LN. However, more well-designed studies with large sample size are needed to validate this association.

Keywords: Systemic lupus erythematosus (SLE), lupus nephritis (LN), meta-analysis, programmed cell death 1 (PDCD1), polymorphism

Introduction

Systemic Lupus Erythematosus (SLE) is a type of immune-mediated destruction which is characterized by the breakdown of self-tolerance and the deposition of circulating immune complexes [1]. Lupus nephritis (LN) is one of the most common complications of SLE. It is well established that genetic, hormonal and environmental factors are implicated in SLE, specifically, imbalances of these interactions determine the onset of SLE. Nevertheless, the pathogenesis of SLE remains incompletely understood.

Family studies, twin studies and segregation analyses have been applied into providing an evidence for the strong role of susceptibility genes in the etiology of SLE [2]. A genome-wide scan has revealed a significant linkage of chromosome 2q37 with susceptibility to SLE. The programmed cell death 1 (PDCD1 or PD-1) gene loci is located on chromosome 2q37, its important functions had been shown through PDCD1 knocking out mice [3-5]. It is an immune inhibitor receptor, with an important function in modulating the activation of lymphocytes through interacting with its widely expressed ligands [6, 7].

Many studies have examined the potential contribution of PDCD1 genes ingle nucleotide polymorphisms (SNPs) to SLE susceptibility, however, the results remain controversial and inconclusive [8-10]. Wang *et al* pointed out that PDCD1 SNPs have a contact with susceptibility to SLE in Europeans and Mexicans and

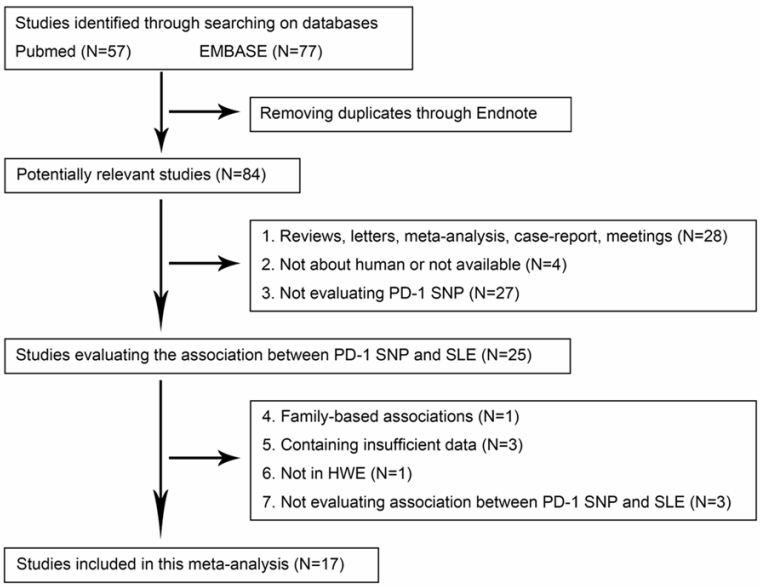

Figure 1. Flow chart of articles selection.

also associates with renal manifestations in SLE patients from northern Sweden [4, 11]. The association of PD-1.3A/G SNPs (located in intron 4, position 7146, also known as rs11568821) with susceptibility to SLE has been replicated in cohorts of SLE patients from different ethnicities [12-14]. Prokunina *et al* suggested that PD1.3A was a risk factor in the development of SLE while another study from Spain hold an opposite opinion that PD1.3A allele might be a protective factor in SLE susceptibility [15]. A modest association of the A allele with the risk of SLE in European Americans was observed while no association with SLE susceptibility in Spain population [14, 15]. Although a meta-analysis about associations of PDCD1 SNPs with SLE and LN has been published, the number of included studies were relatively small. Furthermore, PD1.3A/G polymorphism does not explain all of the PDCD1 SNPs associations with SLE. Therefore, in this study, we explored the associations of all available PDCD1 SNPs including PD1.3, PD1.5, PD1.1 and PD1.6 SNPs with SLE and LN through a meta-analysis.

Methods

Search strategy for the association of PDCD1 gene polymorphism with SLE and LN risk

In order to identify all available studies, a detailed search pertaining to associations of PDCD1 SNPs with susceptibility to SLE was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. A prespecified search strategy was applied to search all English-language literatures in Pubmed and EMBASE (up to September 2015). Literature search was performed using the following search terms "PDCD1", "PD-1", "programmed death 1" together with "polymorphism", "SNP", or "SLE", "system lupus erythematosus" both as medical subject headings (MeSH) and text words without restricting on race, ethnicityor geographic area. Additionally, all the references in the retrieved literatures were manually reviewed to identify other potential relevant articles.

Inclusion and exclusion criteria

Studies fulfilling the following inclusion criteria were included in this meta-analysis: (1) unrelated case-control study on association between PDCD1 SNPs and SLE or LN; (2) the recruited patients fulfilled the American College of Rheumatology 1997 Revised Criteria or the American College of Rheumatology (ACR) Criteria for SLE [16, 17]; (3) with sufficient published data for us to calculate odds ratio (OR) with 95% confidence interval (95% CI); (4) the genotype distribution of the control population was in Hardy-Weinberg equilibrium (HWE); (5) cases and controls should be well matched on ethnicity and geography. When a study examined different populations, we treated each population as a separate study. On the other hand, a study must be excluded if it fulfills the following criteria: (1) it is not about human or it is based on family association study; (2) it is not available for us to calculate OR containing over lapping or insufficient data; (3) it is a review, letter, case-report, meeting or meta-analysis; (4) it did not evaluate the association of PDCD1 SNPs with susceptibility to SLE. The process of selecting relevant articles is shown in **Figure 1**.

Data extraction and synthesis

The following information containing first author name, publishing years, sample sizes as well as the number of genotype and allele

Table 1. Basic characteristics of individual studies included in this meta-analysis

Studies	Population	NOS	SLE	Control	Matched criteria	Studied polymorphisms	Association findings
Chua (2015) [23]	Malay	7	70	70	Ethnicity, age	PD1.1, 3, 5, 6	PD1.5, P<0.01
	Indian		15	15	Ethnicity, age	PD1.1, 3, 5, 6	PD1.5, P<0.01
Ferreiros-Vidal (2007) [25]	Germany	7	100	100	Ethnicity	PD1.3	NS
	Czech		101	100	Ethnicity	PD1.3	NS
	Hungary		94	98	Ethnicity	PD1.3	NS
	Milan		127	196	Ethnicity	PD1.3	NS
	Rome		76	99	Ethnicity	PD1.3	NS
	Naples		81	216	Ethnicity	PD1.3	NS
	Greece		197	377	Ethnicity	PD1.3	NS
Ferreiros-Vidal (2004) [39]	Spain	7	518	800	Ethnicity	PD1.1, 2, 3, 4, 5, 6, 9	PD1.3, P<0.01
Johansson (2005) [40]	Sweden	7	260	670	Ethnicity, age, sex	PD1.3	NS in SLE vs controls
	Sweden		86	174	Ethnicity, age, sex	PD1.3	P=0.005 in LN vs non-LN
Nielsen (2004) [18]	Denmark	7	95	155	Ethnicity	PD1.3, 4, 5, 6 PD+6867, +7209	PD1.4, P=0.016 PD+6867C, P=0.021 in LN vs Non-LN
Prokunina (2002) [13]	Swedish	7	263	235	Ethnicity	PD1.3,5,6	PD1.3, P=0.005; PD1.5, P=0.008
	Mexican		402	149	Ethnicity	PD1.3,5,6	PD1.3, P=0.0009
Prokunina (2004) [9]	Sweden	7	154	356	Ethnicity	PD1.3	PD1.3, P=0.002
	US		82	366	Ethnicity	PD1.3	NS
Sanchez (2011) [30]	African-American	7	1478	1725	Ethnicity	PD1.3	NS
Sanghera (2004) [14]	European American	7	276	359	Ethnicity	PD1.3	NS
	African-American		35	31	Ethnicity	PD1.3	NS
Velazquez-Cruz (2007) [31]	Mexico	8	250	355	Ethnicity, sex	PD1.3, 5, 6	PD1.3A, P<0.01; NS in LN vs non-LN
Wang (2006) [32]	Taiwan	8	109	100	Ethnicity, age, sex	PD1.1, 2, 3, 4, 5, 6, 9 PD+5708, +7209	PD+7209C, P=0.002
Mostowska (2008) [37]	Polish Caucasian	7	102	140	Ethnicity, age, sex	PD1.2, 3, 6, +5708, +7209	PD+7209, P=0.0017
Canto (2010) [22]	Brazil	6	95	128	Ethnicity	PD1.3	NS
Bertsias (2009) [24]	Greece	8	289	256	Ethnicity, age, sex	PD1.3	P=0.006
Hughes (2012) [26]	European descent	6	3936	3491	Ethnicity	PD1.3	NS
Lin (2004) [29]	Chinese	7	98	100	Ethnicity, sex	PD1.5	NS
Wang (2008) [41]	Chinese	7	122	143	Ethnicity, sex	PD+7872, +8162	PD+7872, P=0.025, PD+8162, P=0.023

Abbreviations: NS: not significant; LN: lupus nephritis; non-LN: cases without lupus nephritis.

both on controls and cases, ethnicity, HWE and matched criteria were extracted from individual eligible articles according to the meta-analysis of observational studies in epidemiology (MOOSE) guidelines for reporting an analysis of observational studies [18]. If the number of alleles or genotypes was not available for us, we obtained the numbers by the number of total experimental and control groups via a genetic calculating method (number of genotypes = frequency multiplied by total sample size; number of allele = frequency multiplied by two times of total sample size). Data from each selected study were independently extracted by two authors and consensus for all data was finally reached via discussion. The characteristics of eachstudy from which data were extracted are shown in **Tables 1**-**3**.

Assessment of methodological quality

The quality of individual studies was assessed according to the Newcastle-Ottawa Scale (NOS) (Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). A star system of the NOS has been developed to evaluate the quality of case-control and cohort studies (ranging from 0 to 9 stars). The mean value for the included studies was approximately seven stars and the quality of individual studies was shown in **Table 1**.

Statistical analysis

Allele frequencies of the PDCD1 polymorphisms from individual studies were determined by the allele counting method. The association between the PDCD1 SNP and SLE was compared using the OR corresponding to 95% CI. The distribution of genotypes in control groups from corresponding studies conformed to the HWE except for one study as detected by the chi-squared test (significance set to $P<0.05$) [19]. $P<0.05$ was considered statistically significant through the Z test to calculate the summary ORs. A chi-squared-based Q-statistic test was used to detect the heterogeneity, whose calculating method is $100\% \times (Q\text{-}df)/Q$, ranging from 0 to 100% and representing the proportion of between-study variability, additionally, low, moderate and high levels were used to define I^2 values as 25, 50 and 75% respectively [20]. A random effect model (DerSimonian and Laird method) was used when there existed heterogeneity at the level of $P<0.05$ or $I^2 \geq 50\%$, otherwise, a fixed model (Mantel-Haenszel method) was applied. All statistical analysis for this meta-analysis wasperformed through STATA version 12.0 (Stata Corporation, College Station, TX, USA).

Evaluating publication bias

The potential publication bias was estimated using the funnel plot, in which the standard error of log (OR) of each study was plotted against the respective log (OR) whose results were shown in the funnel plot carried out by Begg's test. A potential publication bias was suggested by an asymmetric funnel plot or determined by the *t*-test suggested by Egger's linear regression at the level of less than 0.05. We used the trim and fill method to identify and adjust the summary estimate for the observed publication bias when asymmetry was indicated. This method removes small studies until achieving symmetry of the funnel plot and estimates the number of missing studies to calculate an adjusted odd ratios (ORs) and 95% CI for the corresponding studies. A revised summary estimating is then calculated using all of the original studies, together with the hypothetical 'filled' studies, subsequently the effect values before and after the trim and fill method were then compared to assess the stability of our analysis [21].

Results

Articles included in this meta-analysis

25 eligible case-control studies concerning the association of PDCD1 SNPs with susceptibility to SLE were identified through searching on Pubmed and EMBASE [8-10, 12-15, 18, 19, 22-37]. Onebeing family-based [12], three containing insufficient data [8, 27, 28], three not evaluating association of PD-1 SNPs with SLE [33, 34, 36], one not in HWE [19] were excluded. If a study is reported on different populations, we treated them as a separate study. Finally 17 articles were included in our analysis among which three studies only provided minor allele frequency (MAF) or genotype frequency, the number were not available, which we got the number of allele and genotype according to the number of total cases and controls by genetic calculating method [22, 24, 26]. A subgroup analysis was utilized only if it was studied based on more than two comparisons.

Evaluation of study quality and sensitivity analysis

In the recruited studies, the genotype distribution of the PDCD1 polymorphismsin control

Table 2. Data extraction of individual studies included in this meta-analysis

	Studies	Country	Ethnicity	Genotype						Allele				HWE
				Case			Control			Case		Control		
				AA	AG	GG	AA	AG	GG	A	G	A	G	
PD1.1	Mahmoudi (2015)	Iranian	Asian	0	6	44	0	6	196	6	94	6	398	NS
	Chua (2015)	Malay	Asian	8	27	35	7	33	30	43	97	47	93	NS
	Wang (2006)	Taiwan	Asian	43	45	21	35	40	25	131	87	110	90	NS
	Chua (2015)	China	Asian	28	53	34	28	53	34	109	121	109	121	NS
PD1.3	Sanghera (2004)	European American	Caucasian	3	65	208	4	69	286	71	481	77	641	NS
	Mostowska (2008)	Caucasian	Caucasian	3	17	82	5	28	107	23	181	38	242	NS
	Ferreiros-Vidal (2007)	Germany	Caucasian							30	170	22	178	NS
	Ferreiros-Vidal (2007)	Czech R	Caucasian							19	183	11	189	NS
	Ferreiros-Vidal (2007)	Hungary	Caucasian							29	159	22	174	NS
	Ferreiros-Vidal (2007)	Milan	Caucasian							31	223	42	350	NS
	Ferreiros-Vidal (2007)	Rome	Caucasian							15	137	29	169	NS
	Ferreiros-Vidal (2007)	Naples	Caucasian							21	141	49	383	NS
	Ferreiros-Vidal (2007)	Greece	Caucasian							50	344	80	674	NS
	Ferreiros-Vidal (2004)	Spain	Caucasian							97	939	206	1394	NS
	Johansson (2005)	Sweden	Caucasian	2	34	224	1	72	597	38	482	74	1266	NS
	Nielsen (2004)	Denmark	Caucasian	2	18	75	0	21	134	22	168	21	289	NS
	Prokunina (2002)	Swedish	Caucasian							56	470	36	434	NS
	Chua (2015)	Indian	Caucasian	0	1	14	0	1	14	1	29	1	29	NS
	Prokunina (2002)	Mexican	Latin							58	746	7	291	NS
	Velazquez-Cruz (2007)	Mexico	Latin	0	26	224	0	14	341	26	474	14	694	NS
	Sanghera (2004)	African-American	African	0	7	28	0	3	28	7	63	3	59	NS
	Sanchez (2011)	African-American	African							78	2878	69	3381	NS
	Wang (2006)	Taiwan	Asian	1	5	103	1	7	92	7	211	9	191	NS
	Chua K (2010)	Malay	Asian	0	1	69	0	1	69	1	139	1	139	NS
	Canto (2010)	Brazil	Caucasian							18	172	20	236	NS
	Bertsias (2009)	Greece	Caucasian	2	87	200	2	47	207	91	487	51	461	NS
	Hughes (2012)	European	Caucasian							882	6990	824	6158	NS
PD1.6	Chua (2015)	China	Asian	52	49	14	47	55	13	155	77	149	81	NS
	Chua (2015)	Malay	Asian	18	33	19	14	35	21	69	71	63	77	NS
	Chua (2015)	Indian	Caucasian	2	2	11	0	4	11	6	24	4	26	NS
	Nielsen C (2004)	Denmark	Caucasian	1	17	77	0	10	47	19	171	10	104	NS
	Prokunina (2002)	Swedish	Caucasian							44	482	41	425	NS
	Mostowska M (2008)	Polish	Caucasian	4	22	76	5	29	106	30	174	39	241	NS
	Prokunina (2002)	Mexican	Latin							338	374	62	52	NS
	Velazquez-Cruz (2007)	Mexico	Latin	70	125	55	118	165	72	265	235	401	309	NS
PD1.5				CC	CT	TT	CC	CT	TT	C	T	C	T	
	Chua (2015)	China	Asian	56	49	10	46	60	9	161	69	152	78	NS
	Wang (2006)	Taiwan	Asian	62	42	5	47	47	6	166	52	141	59	NS
	Lin (2004)	China	Asian	54	37	7	55	40	5	145	51	150	50	NS
	Chua (2015)	Malay	Asian	25	42	3	44	21	5	82	48	109	31	NS
	Nielsen (2004)	Denmark	Caucasian	32	54	9	21	27	9	118	118	69	45	NS
	Prokunina (2002)	Swedish	Caucasian							316	210	154	118	NS
	Prokunina (2002)	Mexican	Latin							439	365	74	46	NS
	Velazquez-Cruz (2007)	Mexico	Latin	102	119	29	150	155	50	323	177	455	255	NS

Abbreviations: NS: not significant; HWE: Hardy-Weinberg equilibrium.

groups was well consistent with the HWE, except for one study from Mahmoudi *et al* which may play a great role in contributing to potential publication bias. However, there was evidence of publication bias in the meta-analyses for the PD1.3A as well as PD1.6 polymorphism in overall and in Caucasian groups (Egger's regression test at the level of $P<0.05$) as shown in **Table 4**. Therefore, the trim and fill method was used to adjust the publication bias and to calculate the estimated OR and 95% CI as shown in **Figures 2-5**.

Table 3. Characteristics of studies based on lupus nephritis

Studies	Country	Ethnicity	Allele			
			Case with LN		Control without LN	
			A	G	A	G
Johansson (2005)	Sweden	Caucasian	21	151	17	331
Prokunina (2004)	Sweden	Caucasian	27	281	27	685
Prokunina (2004)	US	Caucasian	9	155	39	693
Nielsen (2004)	Denmark	Caucasian	8	54	14	114
Velazquez-Cruz (2007)	Mexico	Latin	11	181	6	112

Abbreviations: LN: lupus nephritis.

Table 4. Statistics of publication bias in Egger's test

Comparison			Egger's test
PD1.3	Overall	A vs G	0.012
		AA+AG vs GG	0.784
		AA vs GG+AG	0.664
	Caucasian	A vs G	0.041
		AA+AG vs GG	0.731
		AA vs GG+AA	0.185
PD1.5	Overall	C vs T	0.418
		CC+CT vs TT	0.676
		CC vs CT+TT	0.606
	Asian	C vs T	0.116
		CC+CT vs TT	0.264
		CC vs CT+TT	0.062
	Caucasian	C vs T	0.656
PD1.6	Overall	A vs G	0.078
		AA+AG vs GG	0.006
		AA vs GG+AG	0.162
	Caucasian	A vs G	0.098
		AA+AG vs GG	0.043
		AA vs GG+AA	0.055
PD1.1	Overall	A vs G	0.229
		AA+AG vs GG	0.078
		AA vs GG+AG	0.486
	Asian	A vs G	0.611
		AA+AG vs GG	0.951
		AA vs GG+AA	0.486
LN	Overall	A vs G	0.136
	Caucasian	A vs G	0.264

Abbreviation: LN: lupus nephritis.

Evaluation of the PD1.3A/G polymorphisms with susceptibility to SLE and LN

The summary for the association of PDCD-1.3A/G polymorphisms with susceptibility to SLE and LN is shown in **Table 5**. An association was observed between PD1.3A/G and SLE risk in the overall population (OR=1.243, 95% CI=1.064-1.452, *P*=0.006), however, after applying the trim and fill method, the adjusted OR and 95% CI was not significant (OR=1.142, 95% CI=0.978-1.335, *P*=0.093). When stratified by ethnicity, the results suggested an association of PD1.3A allele with susceptibility to SLE in Latin population (OR=2.961, 95% CI=1.776-4.936, *P*<0.001), in addition, an association between PD1.3AA+AG genotype and SLE was found in Caucasian population (OR=1.389, 95% CI=1.133-1.703, *P*=0.002). However there was no significant association for the PD1.3A allele with SLE in Asian and African populations. Additionally, the results of this meta-analysis also revealed that PD1.3A/G polymorphism was significantly associated with LN risk both in overall and Caucasian population (Overall: OR=1.776, 95% CI=1.290-2.444, *P*<0.001; Caucasian: OR=1.873, 95% CI=1.341-2.616, *P*<0.001) (as **Table 5** shown).

Evaluation of the PD1.1, PD1.5 and PD1.6 polymorphisms with susceptibility to SLE

No significant association was found between PD1.5C/T polymorphism and SLE in overall, Caucasian and Asian population (overall: OR=1.010, 95% CI=0.888-1.149, *P*=0.878; Asian: OR=0.979, 95% CI=0.685-1.400, *P*=0.909; Caucasian: OR=1.010, 95% CI=0.862-1.183, *P*=0.906). The pooled OR for PD1.6A/G polymorphism was 0.945 in overall population, however, after stratification by ethnicity, sensitivity did not increase, the same results were detected in PD1.1 polymorphism either through fixed model or the trim and fill method (**Table 5**).

Discussion

It is widely identified that PDCD1 is a member of CD28/B7 family, with an important function in inhibiting the activation of lymphocytes through interacting with its widely expressed ligands [6, 7]. The negative costimulatory functions of PDCD1 were suggested by the studies on PD-1 deficient mice which exhibited hyperactivation of the immune system and subsequently developed different kinds of autoim-

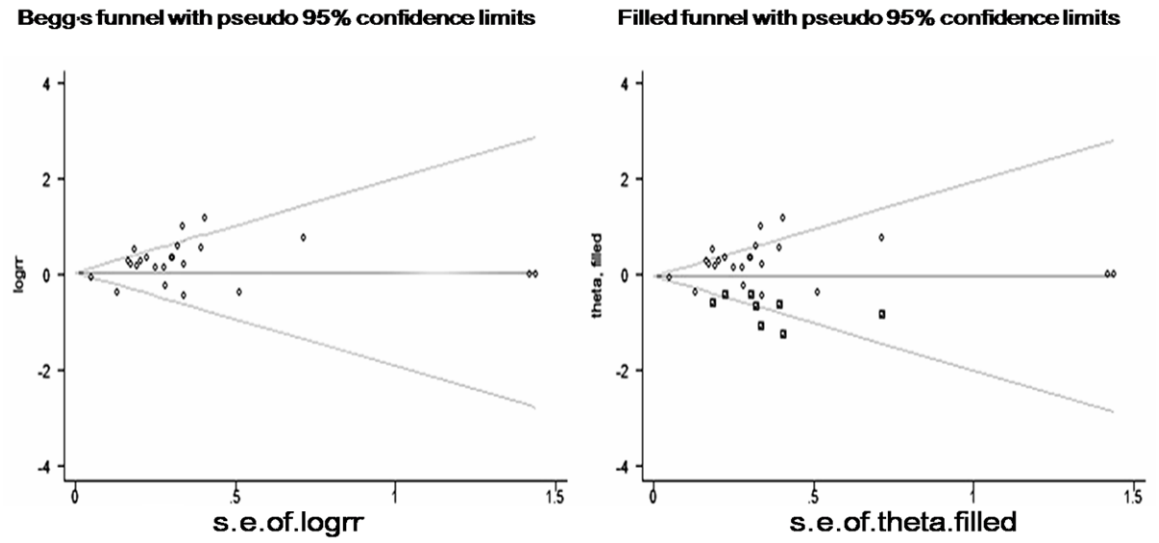

Figure 2. Funnel plot with 95% CI of studies on PD1.3A/G polymorphism and SLE by the trim and fill method in overall populations.

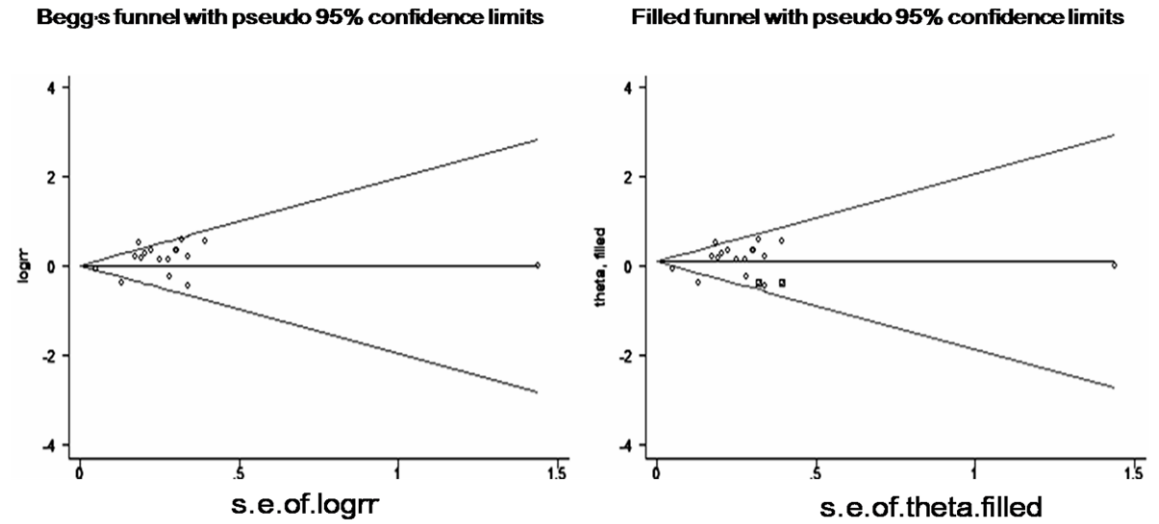

Figure 3. Funnel plot with 95% CI of studies on PD1.3A/G polymorphism and SLE by the trim and fill method in Caucasian populations.

mune diseases on the genetic background [4]. Compared with healthy controls, the PDCD1 expression levels of SLE patients were significantly increased and the upregulated PDCD1 expression levels were positively associated with SLEDAI scores [27]. Additionally, PDCD1 SNPs were involved in the development of SLE, Graves' disease and rheumatoid arthritis (RA) [4]. Until now, the link between PDCD1 SNPs and SLE and the results remain controversial and inconclusive.

Prokunina L, *et al* suggested that PD1.3A/G was associated with the development of SLE [13]. However, another study hold an opposite opinion that PD1.3A allele played a protective role in SLE susceptibility [15]. In our meta-analysis, an association between SLE and the PD1.3A/G polymorphism was found in the overall populations, but there existed significant inter-study heterogeneity. The association remained non-significant after using the trim and fill method to adjust publication bias. The

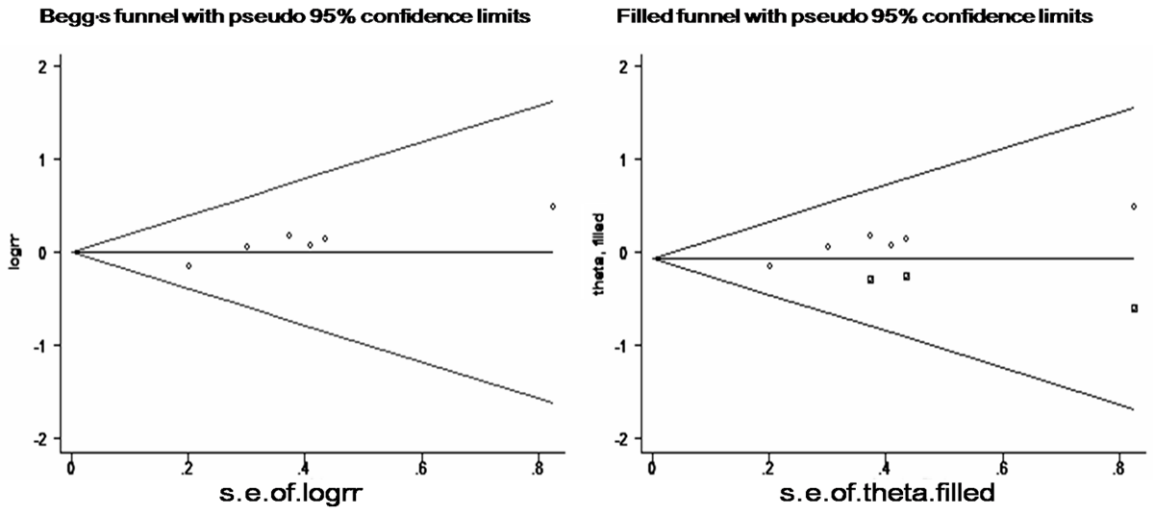

Figure 4. Funnel plot with 95% CI of studies on PD1.6 AA+AG/GG polymorphism and SLE by the trim and fill method in overall populations.

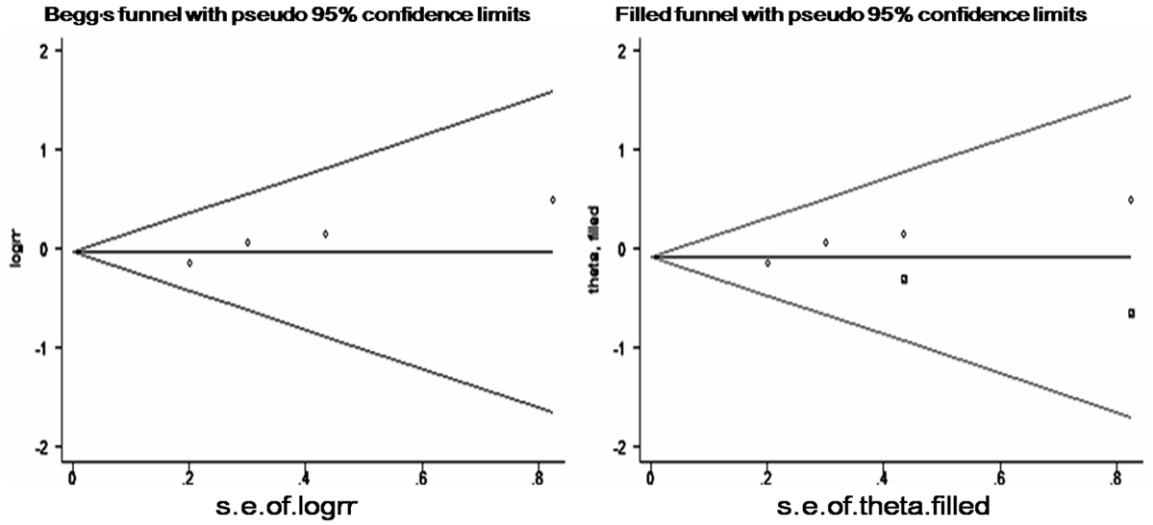

Figure 5. Funnel plot with 95% CI of studies on PD1.6 AA+AG/GG polymorphism and SLE by the trim and fill method in Caucasian populations.

association between the PD1.3A/G polymorphisms and SLE patients was not discovered in Caucasian, Asian, African populations, but the PD1.3A/G poly morphism was significantly associated with susceptibility to SLE in Latin Americans. Furthermore, the PD1.3A allele was a risk factor for LN in both in overall and Caucasian populations. For the PD1.5C/T polymorphism with SLE, no association was found in overall, Caucasian and Asian population. The pooled OR for PD1.6A/G polymorphism was 0.945 in overall populations, however after stratification by ethnicity, sensitivity did not increase, the same results were detected in PD1.1A/G polymorphism either through fixed model or the trim and fill method. In conclusion, it is not clear if the PD1.3A/G poly morphisms confer an association with susceptibility to SLE, but it seems that the PD1.3A allele is a risk factor for SLE in Latin population and LN in overall and Caucasian populations, which suggested that PDCD1 plays an important role in the pathogenesis of SLE and LN. One possibilityis that PDCD1 might play an essential role in maintaining and controlling central and peripheral tolerance through limiting the activation of

Table 5. Meta-analysis of associations between PDCD1 SNPs and SLE or lupus nephritis

	Population	Comparison	Sample size		Number of study	Test of association			Model	Test of heterogeneity		
			Patients	Controls		OR	95% CI	*P*		*Q*-value	*P*	I^2
PD1.3	Overall	A vs G	17938	19730	23	1.243	1.064-1.452	0.006	R	55.13	0.000	60.1%
		A vs G*			31	1.142	0.978-1.335	0.093	R			
		AA+AG vs GG	1501	2151	10	1.453	1.203-1.755	<0.001	F	12.33	0.195	27.0%
		AA vs AG+GG	1501	2151	10	1.335	0.628-2.835	0.453	F	3.45	0.631	0.0%
	Asian	A vs G	358	340	2	0.733	0.285-1.888	0.520	F	0.05	0.816	0.0%
	Caucasian	A vs G	13250	14870	17	1.156	0.992-1.348	0.064	R	35.39	0.004	54.8%
		A vs G*			19	1.116	0.964-1.293	0.142	R			
		AA+AG vs GG	1037	1595	6	1.389	1.133-1.703	0.002	F	5.96	0.310	16.2%
		AA vs AG+GG	1037	1595	6	1.375	0.629-3.009	0.425	F	3.39	0.494	0.0%
	African	A vs G	3026	3512	2	1.366	0.993-1.878	0.055	F	0.46	0.497	0.0%
	Latin	A vs G	1304	1008	2	2.961	1.776-4.936	<0.001	F	0.11	0.744	0.0%
PD1.5	Overall	C vs T	2804	1988	8	1.010	0.888-1.149	0.878	F	10.66	0.154	34.3%
		CC+CT vs TT	737	797	6	1.209	0.854-1.712	0.285	F	2.16	0.827	0.0%
		CC vs CT+TT	737	797	6	0.945	0.656-1.361	0.761	R	14.08	0.015	64.5%
	Asian	C vs T	784	770	4	0.979	0.685-1.400	0.909	R	7.58	0.055	60.4%
		CC+CT vs TT	392	385	4	1.015	0.572-1.801	0.959	F	1.18	0.758	0.0%
		CC vs CT+TT	392	385	4	0.942	0.508-1.744	0.848	R	13.82	0.003	78.3%
	Caucasian	C vs T	2020	1216	4	1.010	0.862-1.183	0.906	F	3.08	0.380	2.5%
PD1.6	Overall	A vs G	2532	2084	8	0.945	0.818-1.093	0.447	F	4.11	0.767	0.0%
		AA+AG vs GG	647	752	6	0.985	0.757-1.282	0.913	F	0.52	0.991	0.0%
		AA+AG vs GG*			9	0.946	0.748-1.198	0.647	F			
		AA vs AG+GG	647	752	6	0.969	0.744-1.263	0.816	F	4.25	0.514	0.0%
	Asian	A vs G	370	370	2	1.122	0.833-1.511	0.448	F	0.09	0.759	0.0%
	Caucasian	A vs G	2162	1714	6	0.896	0.759-1.058	0.196	F	2.34	0.800	0.0%
		AA+AG vs GG	462	567	4	0.969	0.717-1.310	0.840	F	0.31	0.958	0.0%
		AA+AG vs GG*			6	0.926	0.700-1.225	0.589	F			
		AA vs AG+GG	462	567	4	0.835	0.597-1.167	0.291	F	1.99	0.574	0.0%
PD1.1	Overall	A vs G	688	974	4	1.100	0.874-1.386	0.415	F	6.61	0.085	64.6%
		AA+AG vs GG	344	487	4	1.134	0.805-1.599	0.471	F	7.24	0.065	58.6%
		AA vs AG+GG	344	487	4	1.114	0.759-1.635	0.581	F	0.21	0.899	0.0%
	Asian	A vs G	588	570	3	1.049	0.829-1.327	0.691	F	1.21	0.546	0.0%
		AA+AG vs GG	294	285	3	1.017	0.710-1.456	0.928	F	1.70	0.427	0.0%
		AA vs AG+GG	294	285	3	1.114	0.759-1.635	0.581	F	0.21	0.899	0.0%
LN	Overall	A vs G	898	2038	5	1.776	1.290-2.444	<0.001	F	6.25	0.181	36.0%
	Caucasian	A vs G	706	1920	4	1.873	1.341-2.616	<0.001	F	5.37	0.147	44.2%

Abbreviations: LN: lupus nephritis; *: adjusted using the trim and fill method; OR, odds ratio; CI, confidence interval; R, random-effects model; F, fixed-effects model.

auto-reactive lymphocytes. Therefore, numerous of research focusing on identifying associations in different ethnicities will be needed to clarify the association of PDCD1 SNPs with susceptibility to SLE and LN to receive a stable conclusion.

Meta-analysis is a kind of large collection of analysis results from individual studies for the purpose of integrating all the findings to make up for the deficiency of small sample size of each study to increase the statistical power. Thus, a pooled analysis with a large sample size, subgroup analysis and heterogeneity explored was required to be performed to better understand the association of PDCD1 SNPs to susceptibility to SLE and LN. However, several limitations in the meta-analysis needs to be addressed. First, publication bias was presented in the meta-analyses of PD1.3A/G with SLE in overall populations. Numerous of studies are required to confirm the association between PD1.3A/G SNPs and SLE. Second, the numbers of both participants and studies recruited in the ethnicity-specific analysis were small. And only five studies examining association of the PD1.3A/G polymorphism with LN, four studies for the association of the PD1.1A/G polymorphism with SLE. The present studies may not have enough evidence to explain the

association between PDCD1 SNPs and SLE and LN in individual ethnic group. Despite the above limitations, our meta-analysis featured several advantages. First, a large number of controls and cases were pooled from each study, which significantly increased the statistical power compared with individual studies. Second, there are studies suggested that in inducing tolerated lupus-like BWF1 mice, administration with anti-PD-1 Ab could reduce disease manifestations and proteinuria [38]. Our meta-analysis might provide further evidencethatanti-PDCD1 mAb-based therapy may be effective to halt the progress of SLE and LN.

In conclusion, even though significant association between the PD1.3A/G polymorphism and SLE in overall populations was not found, this meta-analysis demonstrates that the PD1.3A allele may confer SLE susceptibility in Latin population and also confer LN susceptibility both in overall and Caucasian populations and our study highlights the importance of having large multiple cohorts when studying a complex disease.

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Disclosure of conflict of interest

None.

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